American Journal of Medical Genetics 68:39–42 (1997)

Brief Clinical Report

Anophthalmia, Intracerebral Cysts, and Cleft Lip/Palate: Expansion of the Phenotype in Oculocerebrocutaneous Syndrome?

Brad Angle* and Joseph H. Hersh
Child Evaluation Center, Department of Pediatrics, University of Louisville, Louisville, Kentucky

We report on a patient with multiple congenital anomalies including anophthalmia, cleft lip and palate, and central nervous system anomalies similar to the case reported by Leichtman et al. [1994: Am J Med Genet 50:39–41] and to oculocerebrocutaneous (Delleman) syndrome. Although the two cases and those with oculocerebrocutaneous syndrome may represent separate but overlapping entities, our patient and the case described by Leichtman et al. [1994: Am J Med Genet 50:39–41] may represent a more severe form of oculocerebrocutaneous syndrome. Am. J. Med. Genet. 68:39–42, 1997

KEY WORDS: anophthalmia; cerebral malformations; cleft lip/palate; oculocerebrocutaneous syndrome; Delleman syndrome

INTRODUCTION

Leichtman et al. [1994] described anophthalmia, bilateral cleft lip and palate, cerebral malformations, and focal dermal defects in a patient who had several findings of oculocerebrocutaneous (Delleman) syndrome but also facial clefts and hypothalamic dysfunction. The authors suggested that their patient might have a severe form of oculocerebrocutaneous syndrome or a new entity.

We report on a patient similar to that of Leichtman et al. [1994] with anophthalmia, cerebral malformations, and cleft lip and palate.

CLINICAL REPORT

N.B. was a 3,745-g Caucasian boy born at 35 weeks of gestation to a 35-year-old mother and a 33-year-old father after an uncomplicated pregnancy. The patient had a normal 3-year-old brother, a cousin with a clubfoot, and another cousin with spina bifida; there was no parental consanguinity.

At birth, the infant was reported to have macrocephaly and was noted to have bilateral anophthalmia and cleft of lip and palate. No skin abnormalities were identified. Cranial computed tomography showed a large intracranial cyst. Chromosome analysis performed on cultured leukocytes and fibroblasts were normal (46,XY). Renal and cardiac ultrasound findings were normal. Myoclonic seizures were noted at age 3 months. A ventriculoperitoneal shunt was inserted at age 4 months for treatment of hydrocephalus.

On physical examination at age 7 months (Fig. 1), the infant's weight was 8.6 kg (>50th<75th centile), length was 68.5 cm (25th centile), and occipitofrontal circumference (OFC) was 54 cm (9 cm >95th centile). Generalized hypotonia was present, and he had no head control. The infant exhibited moderate developmental delay but was responsive to voice and would grasp and bring objects to his mouth. Magnetic resonance imaging of the brain documented a very large midline cyst occupying the posterior half of the cranium, and absent orbits (Fig. 2). Polymicrogyria was noted in the frontal areas of cerebral cortex, and there was absence of the corpus callosum. The cerebellum and brain stem appeared normal, except for slight compression secondary to the cyst.

Other diagnostic evaluations included a normal creatine kinase (CK) and electromyogram (EMG). Muscle biopsy demonstrated fiber type I atrophy. Hearing evaluation was normal.

DISCUSSION

True anophthalmia is a rare malformation which is caused by failure of formation of the optic pit. If some development of the optic vesicles occurs and is arrested at a later stage, microphthalmia may result. Alternatively, early eye formation may subsequently give rise to cystic growth. These growths may obscure or obliterate eye remnants and result in the appearance of or-

*Correspondence to: Brad Angle, M.D., Child Evaluation Center, University of Louisville, 571 South Floyd Street, Suite 100, Louisville, KY 40202.

Received 30 October 1995; Accepted 26 April 1996

Fig. 1. Infant with macrocephaly, anophthalmia, and cleft lip/palate.

bital cysts or may regress, resulting in clinical microphthalmia.

Recently, Leichtman et al. [1994] reported on an infant with anophthalmia, orbital cysts, cutis aplasia, cleft lip and palate, central nervous system anomalies, panhypopituitarism, and hypothalamic defects. The authors suggested that the patient might represent a variant form of oculocerebrocutaneous syndrome or a distinct syndrome involving a midline developmental field defect.

Oculocerebrocutaneous syndrome was first described by Delleman and Oorthuys [1981] in 2 infants with similar malformations including orbital cysts, cerebral malformations, and focal dermal hypoplasia and aplasia. Characteristic cerebral abnormalities include multiple cysts, and in some cases, agenesis of the corpus callosum. Subsequently, additional patients were reported to have the same condition [Delleman et al., 1984; Ferguson et al., 1984; Wilson et al., 1985; Al-Gazali et al., 1988; Giorgi et al., 1989; Bleeker-Wagemakers et al., 1990; Brodsky et al., 1990; Hoo et al., 1991; De Cock and Merizian, 1992].

While the classic eye findings in oculocerebrocutaneous syndrome are orbital cysts with or without microphthalmia, a number of individuals characterized as having oculocerebrocutaneous syndrome with typical brain abnormalities and skin defects have demonstrated other eye abnormalities, including anophthalmia and microphthalmia without orbital cysts [Brodsky et al., 1990; Hoo et al., 1991]. In addition, one case reported by Al-Gazali et al. [1988] had a coloboma of the lateral canthal region and bilateral subconjunctival dermoids. Therefore, patients with this syndrome may manifest a variety of eye findings including complete anophthalmia, microphthalmia, orbital cysts, or a combination thereof.

Recently, Fryns et al. [1995] reported on 2 sibs with bilateral anophthalmia. One of these was a 17-week-gestation female who also had other anomalies, including bilateral cleft lip/palate. Bilateral anophthalmia associated with pituitary and other abnormalities has

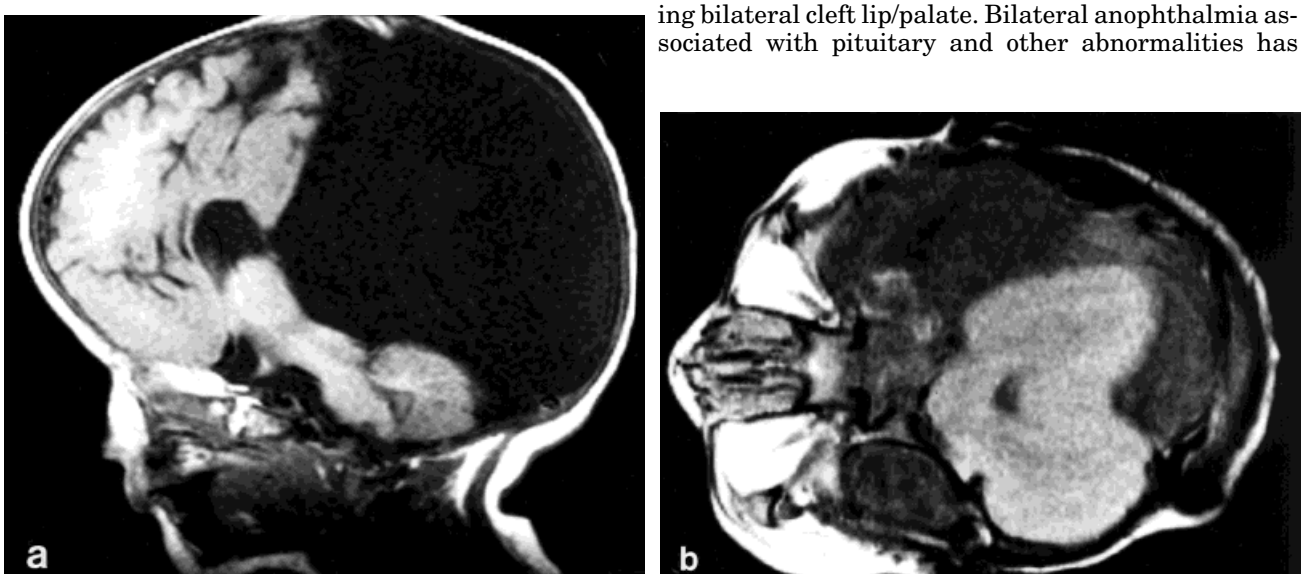

Fig. 2. MRI scan of brain at age 7 months, demonstrating **(a)** large posterior cyst, absence of corpus callosum, and abnormal gyral pattern in frontal lobes and **(b)** absence of orbits bilaterally.

TABLE I. Comparison of Clinical Features of Oculocerebrocutaneous Syndrome (OCC), Leichtman et al. [1994], and Present Case

	OCC	Leichtman et al. [1994]	Present Case
Ocular abnormalites			
Orbital cysts (± microphthalmia)	+	+	−
Anophthalmia	1 case	+	+
CNS malformations			
Intracranial cysts	+	−	+
Absence of corpus callosum	+	−	+
Hydrocephalus	2 cases	+	+
Other anomalies	Cerebellar hypoplasia (1) Cerebral hypoplasia (1) Dandy-Walker (1)	Absent midbrain pedicles Thick hypothalamus Narrow pituitary stalk	Polymicrogyria
Focal dermal defects	+	+	−
Cleft lip/palate	3 cases	+	+

been reported in 2 patients with chromosome abnormalities involving an interstial deletion of 14q [Bennett et al., 1991; Elliott et al., 1993]. However, none of these patients had the brain or skin abnormalities observed in oculocerebrocutaneous (OCC) syndrome.

In addition to OCC, a combination of eye, brain, and skin abnormalities occurs in patients with encephalocraniocutaneous lipomatosis (ECCL). Typical features of ECCL include intracranial cysts with or without calcifications, focal alopecia and/or skin defects, intracranial and subcutaneous lipomas, eyelid defects, and ocular choristoma. Patients with overlapping features of ECCL and OCC have been reported, and the theory that the two conditions might represent the same entity has been reviewed [Loggers et al., 1992; Hennekam, 1994]. Anophthalmia and microphthalmia have been reported in a small number of cases of ECCL, but no patients with cleft lip/palate have been described.

In distinguishing their patient from those with typical oculocerebrocutaneous syndrome, Leichtman et al. [1994] stated that cleft lip and palate, present in their case, previously had not been reported in Delleman syndrome. However, in reviewing published reports, we identified one case with cleft lip and palate [Delleman et al., 1984], and two cases with cleft palate alone [Al-Gazali et al., 1988]. Therefore, orofacial clefting actually appears to represent a low-frequency finding in oculocerebrocutaneous syndrome, and its presence does not exclude a diagnosis of this disorder.

The major clinical manifestations in our patient are bilateral anophthalmia, cerebral malformations, and cleft lip and palate, similar to those manifestations observed in oculocerebrocutaneous syndrome and in the case described by Leichtman et al. [1994] (Table I). The absence of skin defects in our patient represents the only major difference between this case and that of Leichtman et al. [1994] and oculocerebrocutaneous syndrome. Therefore, we suggest that there are sufficient similarities between these patients and previously reported cases of oculocerebrocutaneous syndrome to justify the classification of our patient and the one reported by Leichtman et al. [1994] as severe forms of oculocerebrocutaneous syndrome. In addition, the absence of skin abnormalities in our patient indicates that skin findings, although frequently present, are not obligatory to establish the diagnosis. Identification of other patients with similar findings may provide further clarification of this suggested relationship.

REFERENCES

Al-Gazali LI, Donnai D, Berry SA, Say B, Mueller RF (1988): The oculocerebrocutaneous (Delleman) syndrome. J Med Genet 25: 773–778.

Bennett CP, Betts, DR, Seller MJ (1991): Deletion 14q(q22q23) associated with anophthalmia, absent pituitary, and other abnormalities. J Med Genet 28:280–281.

Bleeker-Wagemakers LM, Hamel BC, Hennekam RCM, Beemer FA, Oorthuys HWN (1990): Oculocerebrocutaneous syndrome. J Med Genet 27:69–70.

Brodsky MC, Harper RA, Keppen LD, Glasier GM (1990): Anophthalmia in Delleman syndrome. Am J Med Genet 37:157–158.

De Cock R, Merizian R (1992): Delleman syndrome: A case report and review. Br J Ophthalmol 76:115–116.

Delleman JW, Oorthuys JWE (1981): Orbital cysts in addition to congenital cerebral and focal dermal malformations: A new entity? Clin Genet 19:191–198.

Delleman JW, Oorthuys JWE, Bleeker-Wagemakers EM, ter Har BGA, Ferguson JW (1984): Orbital cysts in addition to congenital cerebral and focal dermal malformations: A new entity. Clin Genet 25:470–472.

Elliott J, Maltby EL, Reynolds B (1993): A case of deletion 14(q22.1–q22.3) associated with anophthalmia and pituitary abnormalities. J Med Genet 30:251–252.

Ferguson JW, Hutchinson HT, Rouse BM (1984): Ocular, cerebral and cutaneous malformations. Confirmation of an association. Clin Genet 25:464.

Fryns JP, Legius E, Moerman P, Vandenberghe K, Van den Berghe H (1995): Apparently new "anophthalmia-plus" syndrome in sibs. Am J Med Genet 58:113–114.

Giorgi PI, Gabrielli O, Catassi C, Coppa GV (1989): Oculocerbrocutaneous syndrome: Description of a new case. Eur J Pediatr 148:325–326.

Hennekam RC (1994): Scalp lipomas and cerebral malformations: Overlap between encephalocraniocutaneous lipomatosis and oculocerebrocutaneous syndrome. Clin Dysmorphol 3:87–89.

Hoo JJ, Kapp-Simon K, Rollnick B, Chao M (1991): Oculocerebrocutaneous (Delleman) syndrome: A pleiotropic disorder affecting ectodermal tissues with unilateral predominance. Am J Med Genet 40:290–293.

Leichtman LG, Wood B, Rohn R (1994): Anophthalmia, cleft lip/palate, facial anomalies, and CNS anomalies and hypothalamic disorder in a newborn: A midline developmental field defect. Am J Med Genet 50:39–41.

Loggers HE, Oosterwijk JC, Overweg-Plandsoen WCG, Van Wilsem A, Bleeker-Wagemakers EM, Bijlsma JB (1992): Encephalocraniocutaneous lipomatosis and oculocerebrocutaneous syndrome—A differential diagnostic problem? Ophthalmic Paediatr Genet 13:171–177.

Wilson RD, Traverse L, Hall JG, Flodmark CO, Rootman J (1985): Oculocerbrocutaneous syndrome. Am J Ophthalmol 99: 142–148.